REMARKS

Claims 1-9 and 15-26 remain pending.

By the foregoing amendment, applicant has amended each of the independent claims 1 and 3, to recite that the pharmaceutical product as used in the treatment of inflammatory or respiratory disease, further defines the therapeutic agents (i)-(ix) and (xiii) as provided in particulate form "having a particle size from nano-size up to about 12μm", whereas in the therapeutic agents (x)-(xii), 95% of the active particles have a particle size below 2.5μm, and the remaining particles have a particle size of between 2.5 and 5μm. A similar amendment is made to claim 3. Support for each of these amendments can be found in the original disclosure, for example, page 5, fourth full paragraph, (all references to the published WO 004/019985 application). Claim 25 has also been amended to correct a typographical error.

Reconsideration of the previous rejections of claims 1-9, and 15-26, under 35 U.S.C. 102 (e), as being anticipated by Meade et al. (U.S. Patent Publication 2003/0018019 A1) is respectfully requested.

In order to constitute anticipation, the reference must teach every element of the claim.

In fact, the USPTO has promulgated to Examiners exemplary teachings of what does, and does not, constitute anticipation See generally, MPEP Section 2131.
As set forth in this section the Examiners are instructed that "a claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference (citations omitted)." Meade et al. does not anticipate the claimed invention.

As noted hereinabove, in amending the claims, the claims have been amended to recite that the composition is in particulate form, with formulations (i)-(ix) and (xiii)

having a particle size ranging from nano-size up to about 12μm. In particular, there is no explicit disclosure in Meade et al of a pharmaceutical product comprising any of the claimed combination of active ingredients where the active ingredients have a particle size range of from nano-size up to about 12μm, as recited in the present claims. As to formulations (x)-(xii) the particle sizes are specified such that 95% of the active ingredients have a particle size less than 2.5μm and the remaining particles have an particle size in the range 2.5-5μm. Although the Examiner previously argued that the claims are not so limited by particle size, the Examiner is mistaken, because independent claims 1 and 3 (and all dependent claims) contain particle size limitations. Although applicants note the Examiner's generic statement concerning the teachings of Meade et al, there is no teaching in Meade to use the particularly recited combinations, in the particularly recited particle sizes. The disclosure of Meade is completely silent on particular combinations of particle size for triple combinations as specified in the claims. Anticipation requires "identity", not similarity –See MPEP 2131. Thus, there can be no anticipation of the claims by the Meade et al. reference. Withdrawal of the rejection is therefore respectfully requested.

Reconsideration of the previous rejection of claims 1-9, 15-22, and 24-26, under 35 U.S.C. 103 (a), as being unpatentable over Keller et al. (U.S. Patent 6,645,466 B1), is respectfully requested. Keller et al. is concerned with the problem of poor moisture resistance of dry powder formulations. This does not really address the problem of providing improved treatments for inflammatory or respiratory diseases, which is the problem addressed by the present application.

As one skilled in the art would understand, the point of Keller et al. is not to any particular combination of active ingredients, but rather to the generally principle of using magnesium stearate in a dry powder inhalation (DPI) formulation. Although various active ingredients are mentioned, this is really only in passing. Particular

active/combinations of active ingredients are irrelevant to the invention of Keller et al. Rather the invention of Keller et al is a general application to any drug in a (DPI) formulation and, in contrast to the present invention, the particularly recited active ingredients, or combination of active ingredients, are not required. Thus, a skilled person would not have looked to this document in considering the problem solved by this present invention, and it simply does not relate to the field to which the present invention relates, nor have any teachings which would make obvious the instantly recited claimed subject matter, which are specified as particular combinations of active ingredients, in a particulate form, having a particle sizing ranging from about nano-size up to about 12μm for formulations (i)-(ix) and (xiii); and for formulation (x)-(x-ii) 95% of the actives have particle sizes less than 2.5μm, with the remainder of the particle being in the range of 2.5-5 μm.

It appears that the Examiner clearly recognizes the deficiencies in the disclosure of Keller et al., in failing to exemplify a formulation containing each of a beta-mimetic, an anti-cholinergic, and/or a corticosteroid, as noted by the first full paragraph, on page 13 of the Office Action.

Although it is alleged that Keller et al. teach a formulation that can contain two or more pharmaceutically active compounds, such is neither a teaching nor a suggestion of the claimed subject matter. Keller et al. is simply insufficient to establish as obvious the claimed invention at the time the invention was made. One skilled in the art would not know with particularity how to arrive at the claimed subject matter from the teachings of Keller et al. While applicant has specified (and exemplified) various active ingredient combinations, Keller et al. does not do so. Applicants have provided an enabling disclosure for particularly described combination of 3-in-1 formulations in particular particle sizes, while Keller et al. does not provide an enabling disclosure of any 3-in-1 formulations meeting applicant's claims. Thus, Keller et al. simply does not make the

claimed invention obvious to one having ordinary skill in the art. Keller et al. example formulations contain only one active ingredient (and not a combination of three) active ingredients as in the claimed invention. Similarly, all Keller et al. claims are to a formulation containing a single active ingredient only.

Moreover, applicants does not agree the Examiner's view that it would have been obvious to vary the Keller et al. teachings so as to formulate any combination of the active ingredients mentioned therein as aerosol formulations. Keller et al. relates specifically to dry powder formulations and dry powder formulations are the whole point of Keller et al invention. It would therefore not have been obvious to one having ordinary skill in the art to formulate aerosol formulations because to do so would go against the explicit teachings of the document to use dry powders. Moreover, regarding the point about particle size, particle sizes having a size outside the claimed range, do not give satisfactory dose and efficiency. Particles having too large a size fail to penetrate adequately into the lungs. Thus, particles having a specified particle size are required for effective lung penetration, as larger particles are readily trapped in the mouth and/or upper airway passages, and when trapped,the active ingredients are not absorbed therein. In order for the active ingredients to be effectively absorbed, deep lung penetration is required, suitable penetration into the alveoli (i.e., the small air sacs of the lungs) where a very large surface area for absorption is available. All particles having a size above 12 microns, may penetrate to the tracheobronchial regions, in the upper airways, these large particles do not penetrate into the alveoli. Alveolar penetration is, however, achieved with particles within the claimed size range. Thus, the particularly recited particle size range is critical to the claimed invention, and as such particle size range is not found in the cited Meade et al. reference, nor the particular combination of active ingredients found in the Keller et al. teachings, the claimed invention is not obvious and would not have been obvious to the ordinary worker skilled in the art at the time the invention was

made.

In addition, applicants wish to the Examiner to reconsider, as evidence of unexpected and surprising results the previously filed document entitled "A PROOF OF CONCEPT STUDY TO EVALUATE STEPPING DOWN THE DOSE OF FLUTICASONE IN COMBINATION WITH SALMETEROL AND TIOTROPIUM IN SEVERE PERSISTANT ASTHMA" by Tom Fardon et al., Asthma & Allergy Research Group, Division of Medicine Therapeutics Ninewells Hospital & Medical School, University of Dundee, Dundee DDI 9SY, Scotland UK. The triple-active combination of the inventor has been found to give a surprising effect, which could not have been predicted by those having ordinary skill in the art at the time the invention was made. It has been found that in the severe asthmatic patient, lung function can be maintained or improved, but by using less steroid than what would have been normally the case if a triple-active combination was not used. That is to say, the presence two bronchodilators (an anticholinergic agent and ß-2 agonist) working in different ways, when used in a combination with a steroid, have been found to give a "steroid-sparing" effect. In other words, less steroid is needed, which is a desirable result for any steroid treatment.

Evidence of this "steroid-sparing" effect is found in the previously submitted paper which was published in the journal, Respiratory Medicine.

While the study intensively investigates the combination of salmeterol and tiotropium, with the steroid, fluticasone, it shows that the amount of fluticasone may be reduced by half. The conclusion states: "the addition of salmeterol and tiotropium in association with halving the dose of fluticasone propionate in severe asthmatics leads to small improvements and effort dependent and independent pulmonary functions outcomes, but not quality of life scores".

This is actually a surprising result, since tiotropium has not previously been considered effective in asthma treatment (See page 12, second paragraph). This

improvement for severe asthmatics is a surprising and unexpected effected, and would not have been predicted on the basis of any of the cited prior art in the Office Action. It is recognized in the paper that on the basis of the present results, there may now be a role for tiotropium in the treatment of severe asthma (See final paragraph of discussion). This role had not previously been recognized.

The triple-active combination of the present invention also permits a significant reduction in the exhaled level of nitric oxide, in addition to the "steroid-sparing" effect. In this context, applicants refer to page 12, first paragraph of the paper. Nitric oxide is a prominent measure of inflammatory processes in the lungs, and so can be used as a marker for information in asthma. The triple-active combination of the present invention led to suppression of the level of exhaled nitric oxide, and significant improvements of FEVI and FVC, indicating an improvement in lung function. This effect is not seen with simply double-active combinations, for example, it is not seen with fluticasone and salmeterol alone (See second paragraph, page 11). Again this is a surprising effect for the triple-active combination.

It is believed that the effects shown in the attached study are "class" effects-that is, it is believed that these effects are seen with all of the claimed triple-active combinations. These all include two bronchodilators, acting in different ways, together with a steroid. The authors of the enclosed paper state that "the concept of safe step down of inhaled corticosteroid with the addition long-acting brochodilators can be supported in this cohort of severe patients..." See Discussion. It is clear that the results are not specific to any particular combination: The authors believe that there to be a genuine "steroid-sparing class effect", which would be seen with all the claimed combinations. Accordingly, all the claimed combinations of the instant invention, are linked by the same general inventive concept - the combinations share the steroid-sparing effect. Applicants believe that they should be entitled to protect all the specifically

claimed combinations.

In addition, applicants wish to submit additional evidence of unexpected results in the form of a Rule 132 Declaration of Geena Malhotra, one of the co-inventors, reporting the results of experiments conducted under her supervision and control. In order to address the Examiner's views on obviousness, experiments concerning the result of one active ingredient; a combination of two active ingredients; and the claimed combination of three active ingredients, all starting with the same particle size, show the effect on particle size and dosage effectiveness of the claimed triple combination as compared to one; or two components, in combination. It appears that only when the "triple combination" of the invention is made that agglomeration of particles is prevented (paragraph 7 of the Malhotra Declaration) and that the prevention of the agglomeration permits an effective amount of small particles to be administered to the patient.

The applicant has found that the particular anticholinergics present in the claimed combinations (that is, tiotropium, ipratropium and oxitropium) absorb moisture when they are in contact with air and/or propellant. When these actives absorb moisture, the active particles tend to agglomerate, which leads to an increase in particle size. The increase in particle size in turn causes reduced formulation stability and also results in a reduction in fine particle dose (that is, the proportion of particles which reaches the patient's lungs). Ideally, fine particle dose is from 35-40% of the active present in the formulation. However, the applicant has found that in single active formulations containing tiotropium, ipratropium or oxitropium, the fine particle dose is as low as 10 to 20%, and this fine particle dose is further reduced after storing the formulations. The applicant has also found that dose content uniformity for these formulations is poor (around 85% initially) and is further reduced after storage of the formulations. Therefore, the applicant has appreciated a significant problem with formulations comprising these particular actives.

The applicant has also provided a solution to this problem. The applicant has found that when tiotropium, ipratropium and oxitropium are formulated in the particular triple active formulations of the present claims, there is a reduction in the absorption of moisture and a resultant reduction or absence of agglomeration in the final product. Therefore, the triple active combination formulations of the present claims are surprisingly stable, and have an improved fine particle dose, compared to single and double active formulations containing these actives.

The above advantages are demonstrated by the "Supplementary Data" attached to the Malhotra Rule 132 Declaration, as follows:

The data shows fine particle dose and dose content uniformity data for single double, and triple active formulations comprising the anticholinergics employed in the present invention (that is, tiotropium, ipratropium and oxitropium).

Fine Particle Dose

Fine particle dose refers to the proportion of particles having a size suitable for penetration into the alveoli of the lungs. In inhalation formulations comprising anticholinergics, the fine particle dose should be ideally 35-45% of the drug added, with 95% of the particles being below 2.5μm. Only 5% of the particles should be between 2.5 and 5μm.

As shown in the first table in the attached data, the applicant has found that for single active formulations comprising an anticholinergic such as tiotropium, the fine particle dose (FPD) is very low initially, at only 16.67%, and this is further reduced over time – after storage for 1 month at 40°C, the fine particle dose for this formulation was found to be only 10%. It is therefore apparent that the particle size of the active in single active anticholinergic formulations increases over time, with a resultant and deleterious reduction in FPD.

The third table in the attached Supplementary Data shows the fine particle dose

for a double active formulation, comprising the anticholinergic, tiotropium, and formoterol. For the double active formulation, the FPD was improved compared to the single active formulation – the initial FPDs were 34.67% and 40.83% for tiotropium and formoterol respectively; and the FPDs after storage for one month at 40°C were 28.88% and 38.16% respectively. However, the FPDs for this formulation do not meet the ideal FPD criteria set out above, either initially or after storage.

In contrast, it can be seen from the fifth, seventh and ninth tables in the attached Supplementary Data that for triple active formulations according to the present invention, fine particle doses of from around 40% to around 50% are obtained for each active present in the formulations, both initially and after storage for as long as six months at 40°C. Therefore, unlike the single and double active formulations, the triple active formulations of the present invention meet the preferred requirements for fine particle dose. This is a surprising advantage because there is no teaching or indication in any of the prior art documents that improved FPD can be obtained by formulating these particular anticholinergics (or indeed any other drugs) as a particular triple active formulation, as defined in the present claims. Therefore, the skilled person would not have expected this advantage.

Dose Content Uniformity

Dose content uniformity is a measure of the delivered dose compared to the intended dose for an inhalation formulation, and indicates the consistency between doses of a formulation. High dose content uniformity is important for ensuring consistent patient dosing.

It is clear from the second table in the attached Supplementary Data that the dose content uniformity of the single active formulation is undesirably low (only 85%) initially, and that after storage at 40°C for one month it is further reduced, to only 64%.

No improvement in dose uniformity is seen for double active formulations

comprising anticholinergics. As shown in the fourth table in the attached data, dose uniformity for both the actives present in a double active formulation of this type is low – around 60 to 70%, both initially and after storage for one month at 40°C.

However, the applicant has found that – in contrast to the single and double active formulations discussed above – dose content uniformity for all the actives is noticeable improved for triple active formulations comprising the anticholinergics. This is apparent from the sixth, eighth and tenth tables in the attached Supplementary Data, which show that dose content uniformity over 80% is obtained for all the triple active formulations tested, both initially and even after storage at 40°C for as long as six months. This is a significant advantage of the formulations of the present invention.

The problem of dose content uniformity for particular anticholinergic formulations is neither identified nor solved in the prior art – this problem is not even addressed. The improved dose content uniformity seen with formulations of the present invention is unexpected: there is no teaching or suggestion anywhere in the prior art that the poor dose content uniformity seen with single and double active anticholinergic formulations can be improved by formulating triple active formulations.

The skilled person would expect to see the advantages in terms of fine particle dose and dose content uniformity demonstrated for tiotropium formulations in the attached data across all the claimed formulations because each of these formulations comprises one of the anticholinergics tiotropium, ipratropium and oxitropium (which have similar properties) in combination with a betamimetic and a corticosteroid. Therefore, all of the claimed formulations comprise three actives of the same classes as the examples shown in the attached data, so the skilled person would expect these formulations to all share the same properties and advantages.

In summary, therefore, the attached Supplementary Data shows that even after storage for six months, the triple active formulations defined in present claims 1 and 3

have significant and unexpected advantages in terms of dose content uniformity and fine particle dose, compared to double and single active formulations. The particular formulations defined in the claims can therefore be seen to be particularly stable. For the foregoing reasons withdrawal of the prior art rejections are respectfully requested.

Reconsideration and withdrawal of the provisional non-statutory double patenting rejections of the obvious type are respectfully requested. Although it is alleged in the Office Action that the application claim is either anticipated by, or would have been obvious over the referenced claims of co-pending application 11/574,902 (hereinafter "Lulla '902 application") in view of Meade et al., applicants respectfully disagree. As noted above, Meade et al. does not show compositions of formulations (i)-(ix) and (xiii) in particulate form having a particle size from nano-size up to about 12μm. Nor does Meade show formulations (x)-(xii) of the particle sizes specified. Thus, the claims are novel over Meade. Furthermore, the Lulla '902 application does not teach addition of corticosteroids.

As noted in the discussion above with regard to the attached paper, the absence of the steroid is a critical absence in the claimed invention. The claimed invention, in treating inflammatory or respiratory diseases, has a steroid-sparing effect, because of the presence of the two bronchodilators, in combination with the steroid. When no steroid is present, as in Lulla '902, the effect of the present invention would not be seen. Meade et al. does not suggest a composition having the 3-in-1 active ingredient as specifically recited, in combination, with the particle size combination which permits administration of the drug to reach the alveoli because of the particle size range as recited in the claims. Thus, any teachings of Lulla '902 application and/or Meade et al. would be difficult for anticipation, nor make obvious the claimed invention. Accordingly, the applicants respectfully request that the provisional obviousness type double patenting be withdrawn and furthermore note that as the conflicting claims have not in fact been patented, Lulla

'902 is therefore not appropriate as a reference in a double patenting rejection of the obviousness type.

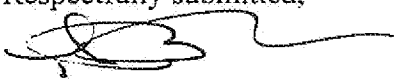
Having fully responded to the preceding Office Action, favorable reconsideration withdrawal of all grounds of rejections set forth therein are respectfully requested and prompt Notice of Allowance are earnestly solicited.

For the foregoing reasons and evidence, favorable reconsideration and withdrawal of the previous rejections and passage of the application to issue are respectfully requested.

The Director is hereby authorized to charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 14-1437, under Order No. 8693.006.US0000.

Date: November 4, 2009

Respectfully submitted,



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